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Case report

DABIGATRAN AND DENTAL EXTRACTIONS

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SUMMARY

For more than 50 years, vitamin K antagonists have been the gold standard in the treatment of cardiovascular and cerebrovascular diseases and in the prevention of their complications. In the last 5 years new anticoagulants dabigatran, rivaroxaban and apixaban are rapidly implemented in the clinical practice, displacing Vit. K antagonists, due to numerous of advantages they have. Dabigatran is the first and most widely used new oral anticoagulant, so it is important for the dentists to be aware of this drug.

The purpose of this article is to review NOA dabigatran, its monitoring and reversal, and provides clinical advice on the management of patients who receives dabigatran and requires dental extractions.

Material and methods: The course of five patients on dabigatran who underwent teeth extraction was assessed. The medical charts of these patients were investigated. Morning dose of dabigatran (Pradaxa) was omitted and teeth extraction was performed ≥12 hours after the last intake of the drug.

Results: Fourteen teeth were extracted in five patients receiving Dabigatran with normal creatinine clearance. Extractions were performed ≥12 hours after the last administration of dabigatran. Only one patient has slightly prolonged bleeding, successfully controlled with local hemostatic measures.

Conclusions: Simple teeth extractions can be safely performed ≥12 hours after the last administration of the medication in patients with normal creatinine clearance without significantly greater bleeding risk than conventional oral anticoagulants. However, currently no established evidence-based guidelines for dental management of these patients are available and further clinical studies are needed.

Keywords: anticoagulants, dabigatran, dental extraction, hemostasis.

INTRODUCTION

In the last 5 years, new anticoagulants have been introduced in the clinical practice, displacing Vit. K antagonists, due to their rapid onset of action, no need for regular monitoring, few drug and food interactions, and a broad therapeutic range (prophylaxis and treatment of pulmonary embolism and venous thrombosis, prophylaxis after orthopaedic surgery; prophylaxis and treatment of thromboembolism associated with atrial fibrillation and/or prosthetic replacement of heart valves; reduction of the risk of death, reinfarction and thromboembolic events after myocardial infarction). [1, 2]

Three types of NOAs have recently been approved for use in the USA and Europe: dabigatran etexilate- direct thrombin inhibitor (DTI), rivaroxaban and apixaban- factor Xa inhibitors (FXaI). A fourth one FXaI, edoxaban, obtained the recent approval of the European MedicinesAgency in Europe (June 2015, 19th). [3]

Dabigatran etexilate (Pradaxa®)

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim, Spain) is the first orally administered direct thrombin inhibitor. It was the first approved NOA in 2008 by the EU and in 2010 by the Food and Drug Administration (FDA). It is a specific, reversible direct thrombin inhibitor that, after oral administration, is rapidly absorbed and converted to its active form, dabigatran, through esterase catalysed hydrolysis in plasma. Mechanism of action of dabigatran is to bind with the active site on free and clot-bound thrombin (factor IIa) so it cannot transform fibrinogen into fibrin. [4] It has a rapid onset of action with a peak plasma concentration at 0.5–4 h. Twenty percent of the absorbed drug undergoes hepatic metabolism, while 80% is excreted unchanged via the renal system, and the dosage must be reduced for patients with renal impairment (CrCl< 50 ml/min). The half - life elimination primarily is determined by renal function and in healthy patients is 12-14 h, 14-17 h in elderly, up to 18 hours in patients with CrCL between 30 and 50 ml/min and up to 27 h in a patient with severe renal dysfunction (creatinine clearance <15–30 ml/min). [5, 6, 7, 8] Creatinine levels should also be considered even the medication is discontinued before a surgical procedure. [7] (Table 1)

Table 1. Direct anticoagulant suspension time according to creatinine clearance value. [9, 10]

Groups	Renal function (Creatinine clearance, mL/min)	Dabigatran half-life (hours)	Timing of discontinuation after last dose of dabigatran before surgery	
			Standard riskbleeding	High risk ofbleeding
Normal	> 80	13 (11-22)	12 hours	2-4 days
Mild renal failure	> 50 to < 80	15 (12-34)	24 hours	2-4 days
Moderate renal failure	> 30 to <50	18 (13-23)	> 48 hours	4 days
Severe renal failure	< 30a	27 (22-35)	2-5 days	> 5 days

Routine monitoring of the anticoagulant effect of dabigatran is not required. In the case of emergency, the thrombin clotting time (TT) and the ecarin clotting time (ECT) are the most sensitive tests for quantifying anticoagulation rate.aPTT is less sensitive, especially for higher doses of dabigatran but because of its broad usage is recommended in case of emergency. [5, 9, 11, 12, 13, 14]

In October 2015, the U.S. Food and Drug Administration approved antidote of dabigatran Idarucizumab, a monoclonal antibody (Praxbind®, Boehringer Ingelheim Pharmaceuticals, Inc., Germany) for the treatment of patients on dabigatran etexilate when reversal of the anticoagulant effect is needed for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding. [15] For minutesIdarucizumab completely reverse the anticoagulant activity of dabigatran in 88 to 98 % of patients. [16]

Drug-drug interactions

Dabigatran has limited clinically significant drug and food interactions. Concomitant intake of Ketoconazole, amiodarone and verapamil may increase the anticoagulant effect of dabigatran, whilst rifampicin may decrease its effect. The risk of bleeding may be increased also by concomitant use of other anticoagulants, antiplatelets, and salicylates.[8] Given that non-cox-selective NSAIDs inhibit platelet aggregation, it may be prudent to avoid their use in patients taking dabigatran. Paracetamol and opioid analgesics are appropriate alternatives. [17]

Risk of Bleeding and dental procedures

The review of the literature reveals only a few published cases of teeth extractions in patients receiving dabigatran.

Breik O, and et al. reported five cases of teeth extractions in patients, receiving dabigartan. The cases of single tooth extractions were managed without drug cessation and there were no significant postoperative bleeding. In case 4 successful extractions of multiple teeth were performed after ceasing dabigatran for 48 hours. Case 5 reports significant postoperative bleeding in a patient who underwent a full-mouth extraction while still taking dabigatran. The bleeding stopped after dabigatran was ceased for 24 hours. They concluded that stopping dabigatran leads to an increased risk of stroke or venous thrombosis, while intraoral bleeding can often be managed with local haemostasis. [18]

Morimoto I, and et al. extracted twenty-three teeth in 19 patients, including two surgical extractions. Among the 19 patients, nine ingested rivaroxaban, six apixaban, and four dabigatran. One patient on rivaroxaban had persistent postoperative bleeding following two surgical extractions. Mild oozing was observed in five patients (two on rivaroxaban and three on apixaban). There were no bleeding episodes in the patients on dabigatran. They concluded that NOAs can usually be continued in patients undergoing tooth extraction. Conversely, patients with a prolonged aPTT (for dabigatran) have a higher risk of bleeding, therefore, adequate local haemostasis and follow-up are required. [12]

Yoshikawa H, and et al. extracted 55 teeth in 19 patients who continued to receive dabigatran. The mean aPTT was 45.4 seconds. In one patient the aPTT was prolonged to more than 70 seconds. All patients underwent tooth extraction 6 to 8 hours after dabigatran intake. Postoperative bleeding occurred in the patient whom aPTT was prolonged to more than 70 seconds. They concluded that measurement of aPTT before extraction is essential and tooth extraction can be performed without cessation of dabigatran if the patient's aPTT is controlled to less than 2 times the reference value. [19]

Weitzet et al. in 2012 published a case study of a patient taking dabigatran which presented bleeding complications. In the article, the authors did a systematic reviewed and included recommendations for minor surgical procedures, such as no drug withdrawal in dental cleanings and extractions, and to do such procedures more than 10 hours after taking the last dose of the drug.[20]

Romond et al. in 2013 published a case report of a patient who had eight dental extractions and pre-prosthetic surgery (alveoloplasty and remodeling of the tuberosity in the maxilla) who was also taking dabigatran. In that case, dabigatran was withdrawn 24 hours before the procedure, and surgery was performed under intravenous sedation and local haemostatic measures were taken, such as the use of local anaesthesia with vasoconstrictor, gelatin sponges, suture and placement of the immediate prosthesis. There was no excessive bleeding or clotting problems in this case. The authors noted that having no agent to reverse the action of dabigatran is sufficient reason for withdrawing the medication when the procedure is more invasive than 2-3 extractions. [13]

Dental considerations

To date, there is no enough evidence-based research to provide a clear protocol for dental treatment in patients, receiving dabigatran. The most current information suggests that patients taking dabigatran can undergo teeth extractions without dose alteration.

Several factors concur in the assessment of bleeding risk during dental treatment in patients receiving dabigatran. These are patient-dependent and surgery-dependent.

Patient-dependent factors are age, renal function, congenital/acquired alterations of the coagulation, intake of antiplatelet or anticoagulant drugs (patients older than 75 years and taking long-term NSAIDs, acetylsalicylic acid, clopidogrel or prasugrel). [14]

Surgery-dependent factors are correlated to the invasiveness and size of the surgery.

Accurate anamnesis and surgical planning are extremely important to intercept these high-risk categories. Actually, the best available protocol regarding discontinuation of dabigatran in elective surgery is that proposed by van Ryn et al. [7] It takes into account the degree of renal function (Table 1), the complexity of the surgical procedure and the patient's risk of bleeding due to other concomitant causes.

For patients requiring simple dental extractions or minor oral surgery procedures (as localised surgical extraction, localised periodontal surgery, apicectomy, incisional biopsy or excision of localised mucosal lesion), it can be assumed that the risk is similar to those in patients taking vitamin k antagonists with an INR < 3. [17]

In the case of elective invasive surgical procedures as multiple surgical extractions, removal of extensive intraosseous lesions or maxillofacial surgery discontinuation of the drug should be considered because some dental patients may have a higher risk of bleeding. [5]. Owing to the risk of thromboembolism, dabigatran should never be discontinued without prior consultation with the treating physician. If discontinuation of anticoagulation is not considered safe, perioperative bridging anticoagulation with an appropriate dose of subcutaneous LMWH or unfractionated heparin is recommended. [5, 17]

In addition, consideration should be given to performing a TT or aPTT6 to 12 hours prior to surgery, which, if normal (30-40 seconds), indicates that the coagulation is normal and that the anticoagulant effect of dabigatran has resolved. [1,7]

Given the rapid onset of action of dabigatran (2 hours) and its relatively short half-life (11.5 hours), is recommended all dental procedures to be scheduled as late as possible after the most recent dose, ideally >12 hours. Scheduling appointment early in the morning of the day and early in the week may be necessary to afford additional visit in case of excessive bleeding. [7, 21]

Local haemostatic measures as absorbable haemostatic dressings such as oxidised cellulose, collagen sponge or resorbable gelatin sponge, should be used routinely in these patients. Also, suturing the extraction sites and pressure application with gauzes with tranexamic acid has also been suggested to prevent postoperative bleeding. [1, 8, 21]

Patients requiring oral/maxillofacial surgery may need discontinuation of drug intake for at least 24 hours pre-operatively, but always in consultation with treating physician. If stopped pre-operatively, NOAs should be recommended when a stable clot or adequate haemostasis has been achieved (typically 6–8 hours postoperatively).When restarting the dabigatran, the anticoagulant effect reaches its optimum level within two hours of administration. [22]

If post-operative bleeding occurs, oral anticoagulant therapy should be stopped, and local haemostatic measures applied. [14, 18]

For patients who experience minor bleeding events, the delaying of the next dose or discontinuation of the drug is indicated although this choice has to be evaluated with prudence considering the possible risk of ischemic events. [17] For moderate or severe bleeding, treatment includes mechanical compression, surgical intervention, fluid replacement, hemodynamic support, oral charcoal application and haemodialysis. For life- threatening bleeding, treatment includes administration of prothrombin complex concentrates, transfusion with packed red cells (PRC) or fresh frozen plasma (FFP), plus haemodialysis +/- rFVIIa if required. [2, 5, 23]

The recent approval of the antidote of dabigatran Idarucizumab will help in solving the concerns related to the absence of a specific reversal agent for dabigatran. [16]

Pain control in the postoperative period

Although dabigatran does not directly interact with NSAIDs, the latter also increase the risk of bleeding. For this reason, prescription of NSAIDs is not preferable and should be made with caution. Alternative drugs for pain management as Paracetamol or opioid medications are safer alternatives for patients taking dabigatran.[17]

Dabigatran acts as a substrate of P- glycoprotein 1 (P-gp 1), a significant protein of the cell membrane that pumps many foreign substances out of cells. The concomitant assumption of strong P-gp 1 inducers like dexamethasone, rifampicin or carbamazepine, has been reported to significantly decrease the plasma concentration-versus-time curve and peak serum concentration of dabigatran. For this reason, these drugs are not recommended in patients taking DTIs. The administration of P-gp 1 inhibitors like ketoconazole (and possibly itraconazole, erythromycin, clarithromycin) should be avoided. [1, 2]

CASES

We report the outcome of five cases of patients, treated with dabigatran who underwent simple teeth extractions. All patients were referred to their treating physician before the dental treatment. According to creatinine clearance value which was normal (> 80 ml/min) in all patients, dabigatran morning dose was omitted in the day of the extraction.

Case 1

Sixty-four year old male referred to the Oral surgery department for extraction of teeth 33. He was taking dabigatran 110 mg twice daily for thromboprophylaxis due to atrial fibrillation. The patient was with I grade hypertension. Tooth 33 was extracted18 hours after the last intake of dabigatran without complication and the sockets were dressed with gelatine sponge and sutured tightly. There was no significant intraoperative or postoperative bleeding.

Case 2

Seventy year old male referred for extraction of tooth27. The patient was with normal blood pressure at the time of treatment.He was taking dabigatran for atrial fibrillation110 mg twice daily. Tooth 27 was extracted14 hours after the last intake of dabigatran. Local haemostatic measures with gelatine sponge and suture were used. No significant intraoperative or postoperative bleeding was observed.

Case 3

Fifty-seven year old female referred for extraction of tooth 24, 28. Her medical history included ischemic heart disease, atrial fibrillation and hypertension. Blood pressure at the time of treatment was 140/90. She was taking 110 mg dabigatran twice daily. Teeth 24, 28 were extracted 16 hours after the last intake of dabigatran and the socket dressed with gelatine sponge and sutured. There was no significant intraoperative or postoperative bleeding.

Case 4

Sixty-one year old male who underwent extraction of seven teeth in five visits: – 14 and 15; 45 and 23; 32 and 42; 12. His medical history included hypertension and atrial fibrillation. Blood pressure at the time of the treatment varied between 120/80 and 140/90.He was taking 110 mg dabigatran twice daily. Teeth were extracted without complication 16 hours after the last intake of dabigatran.Local haemostatic measures with gelatine sponge and suture were used. No significant intraoperative or postoperative bleeding was observed.

Case 5

Seventy-five year old man who underwent extraction of teeth 34, 36 and 37. The patient has a normal blood pressure during treatment. He was taking dabigatran for the prevention of thromboembolism in atrial fibrillation 110 mg twice daily. The teeth were extracted 14 hours after the last dose of dabigatran. Slightly increased intraoperative bleeding was observed, lasted about 10 minutes and successfully controlled with local haemostatic measures with gelatine sponge and suture of the wound. No further postoperative bleeding was reported.

DISCUSSION

There is little information on which to base advice for dentists who need to perform extractions in patients receiving dabigatran.There has been a controversy for years regarding the suspension or alternation of anticoagulant therapy when planning invasive dental procedures. Because of the well-known risk of embolism after suspending antithrombotic medication, physicians tend to be conservative and avoid the suspension of antithrombotic medication.

Otherwise, patients who undergo teeth extractions or invasive procedures are at increased risk of bleeding. Therefore measuring TT or aPTT prior treatment can be informative about the drug plasma levels and for quantifying anticoagulation rate.

Simple teeth extractions can be performed 12 hours after the last administration of the drug, while more extensive surgical interventions may require longer discontinuation of dabigatran. Local haemostatic measures should be used routinely in these patients. If dental extractions are classed as 'moderate or high risk' dabigatran may need to be discontinued, depending on renal function. For procedures with immediate and complete haemostasis, the intake can be resumed 6–8 hours after the intervention.

CONCLUSION

Dabigatran is a direct thrombin inhibitor that is likely to become more widely prescribed.

It is, therefore, incumbent on all of the dentists to become familiar with this drug, its indications, metabolism, excretion and method of action, and, in particular, the management of patients treated with dabigatran who require invasive dental procedures.

In patients with normal renal function taking dabigatran, simple teeth extractions can be safely performed ≥12 hours after the last administration of dabigatran (Pradaxa).

The general dentist should consider referral to an oral and maxillofacial surgeon for patients due to teeth extractions, especially for these with a history of renal impairment, patients requiring multiple extractions, or more complex oral surgical procedures, or patients who are on additional antiplatelet agents or anticoagulants, as there is a higher bleeding risk. Further randomised studies are needed to establish the efficacy and safety of dental extractions in patients receiving dabigatran.

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